Remarks

Applicant thanks Examiner Gina Yu for the courtesy of a telephonic interview on November 6, 2008 with the undersigned attorney. During the interview, the claims were discussed in view of the art cited in the Office action. The substance of the interview is included in this response.

Claims 11, 17, 18, and 29 have been amended. Claim 16 has been cancelled without prejudice to its subsequent reintroduction into this application or introduction into a related application. Upon entry of this paper, claims 11-15, 17, 18, 20, and 27-29 will be pending and under consideration.

Support for the amendment to claim 11 can be found, for example, on page 17, lines 28-29, page 18, Table 1 and page 20, lines 12-13 of the application as filed. Claims 17 and 18 have been amended solely to make the claims more clear; support for these claim amendments can be found, for example, on page 13 of the application as filed. The outstanding rejections are addressed in the order in which they appear in the Office action.

Rejection under 35 U.S.C. § 112, First Paragraph

According to pages 2-3 of the outstanding Office action, claim 29 presently stands rejected under 35 U.S.C. § 112, first paragraph on grounds that it fails to comply with the written description requirement. In particular, the Office Action states, on page 3, "the specification discloses [a] composition comprising 25 mg/ml midazolam on pages 15 and 22, but fails to support compositions containing a higher concentration of midazolam." Without acquiescing to the merits of the rejection, but in order to promote prosecution, claim 29 has been amended to specify that the "composition comprises 25 mg/mL midazolam or a pharmaceutically acceptable salt thereof." Applicant believes that the rejection is rendered moot in view of the claim amendment. Accordingly, Applicant respectfully requests that this rejection be reconsidered and withdrawal.

Rejections Under 35 U.S.C. § 103

According to the Office action, (i) claims 11, 13, 15, 18, 20 and 28 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,166,202 to Schweizer (hereinafter "Schweizer") in view of Hjortkjaer *et al.* in *J. Pharm. Pharmacol.* 1999, 51: 377-383 (hereinafter "Hjortkjaer") and U.S. Patent No. 6,565,832 to Haslwanter (hereinafter "Haslwanter"), (ii) claims 14 and 28 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over Schweizer, Hjortkjaer, and Haslwanter and further in view of U.S. Patent No. 5,554,639 to Craig (hereinafter "Craig"), (iii) claims 16, 17, 20 and 28 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over Schweizer, Hjortkjaer, and Haslwanter and further in view of Fisgin *et al.* (2000) J. Child Neurol. 15:833-835 (hereinafter "Fisgin"), (iv) claim 12 presently stands rejected under 35 U.S.C. § 103(a) as being obvious over Schweizer, Hjortkjaer, and Haslwanter and further in view of U.S. Patent No. 5,789,375 to Mukae (hereinafter "Mukae"), and (v) claim 29 presently stands rejected under 35 U.S.C. § 103(a) as being obvious over Schweizer, Hjortkjaer, and Haslwanter and further in view of Knoester *et al.* (2002) Br. J. Clinc. Pharmacol. 53:501-507 (hereinafter "Knoester").

Claim 16 has been cancelled thereby rendering the rejection of this claim moot. Applicant respectfully traverses the rejections to the extent that they are maintained over claims 11-15, 17, 18, 20, and 27-29, as amended, in view of the following comments.

As indicated above, claim 11 was amended to specify that "the midazolam achieves a time to maximum plasma concentration (T_{max}) within about 10 minutes after intranasal administration." Claims 16 and 17, specifying particular T_{max} values were not rejected based on combinations of Schweizer, Hjortkjaer, Haslwanter, Craig, and Mukae. The Office relies on Fisgin as disclosing "a method of rapidly treating acute seizures of children in 5 minutes by nasally administering midazolam (5 mg/mL)." Office action page 6. The Office alleges on pages 6-7 of the Office action that, in relation to claims 16-17, 20 and 28:

> It would have been obvious to a skilled artisan to formulate and administer the midazolam nasal spray of the combined references as motivated by Fisgin because the latter teaches the time required for midazolam that is nasally administered to take effects. The skilled artisan would have had a reasonable expectation of successfully determining the dosage of midazolam and the time required to treat acute by nasally administering midazolam.[*sic*]

As the Office recognizes, Fisgin does not provide the T_{max} for midazolam administered intranasally as an aqueous solution. Fisgin indicates only that a physiological effect was observed in certain patients following administration of midazolam. The onset of physiological effects in a patient do not necessary correspond to the T_{max} of the therapeutic agent. For example, Burstein *et al.* report that "concentrations [of midazolam] considered adequate to induce sedation were achieved within 7 min of the initiation of drug administration," whereas the T_{max} was 25.8 minutes following intranasal administration of midazolam. See Abstract and page 55 of Burstein *et al.* in *Anesth. Prog.* (1996) 43:52-57. Neither Schweizer, Hjortkjaer, Haslwanter, Craig, nor Mukae cure the deficiencies of Figsin.

The T_{max} of midazolam administered intranasally can be affected by components included in the intranasal pharmaceutical composition. (Declaration of Daniel P. Wermeling, Pharm.D, FASHP, FCCP, Professor in the Pharmacy Practice and Science Department at the University of Kentucky, paragraph 5.) For example, certain components may increase the solubility of midazolam in the intranasal pharmaceutical composition in order to deliver a more concentrated form of midazolam, thereby affecting T_{max}. *Id.* In addition, certain components can affect the nature of the spray (e.g., droplette size and spray plume geometry), which can affect T_{max}. *Id.* Variables, such as these, make it difficult to predict the T_{max} for intranasal delivery of midazolam using certain intranasal pharmaceutical compositions. *Id.*

The art cited by the Office (i.e., Schweizer, Hjortkjaer, Haslwanter, Craig, Mukae, Fisgin, and Knoester) does not teach the particular pharmaceutical composition of claim 11. As amended, claim 11 requires midazolam, propylene glycol, particular amounts of polyethylene glycol, and that the composition is formulated so midazolam has "a time to maximum plasma concentration (T_{max}) within about 10 minutes after intranasal administration." The art cited by the Office provides no guidance on how the presence of propylene glycol will affect the T_{max} of the midazolam composition administered intranasally. (Declaration, paragraph 6.) Further, the art cited by the Office provides no guidance on how the presence and amount of polyethylene glycol will affect the T_{max} of the midazolam composition administered intranasally. (Declaration, paragraph 6.) For example, the midazolam formulation administered to subjects in Schweizer was simply a mixture of midazolam hydrochloride and water. See Schweizer, col. 4, lines 41-42.

In contrast to Schweizer, Example 1 on pages 14-20 of the application as filed describes a midazolam composition containing polyethylene glycol and propylene glycol, and having a mean T_{max} of about 10 minutes when the composition is administered intranasally. This short T_{max} is a significant benefit in therapeutic applications, such as inducing anxiolysis and/or sedation, because it decreases the amount of time the patient suffers from anxiety or the condition requiring sedation.

As provided in the Declaration of Daniel P. Wermeling, Pharm.D, FASHP, FCCP, Professor in the Pharmacy Practice and Science Department at the University of Kentucky, the T_{max} following intranasal administration of a midazolam formulation depends on, for example, the concentration of midazolam in the formulation and the nature of the components making up the formulation. Applicant's formulation in Example 1 on pages 14-20 of the application as filed had a concentration of 25 mg/mL midazolam. Notably, Schweizer and Fisgin, relied upon by the Office, describe much more dilute formulations (5 mg/mL midazolam in water). Furthermore, Applicant's formulation in Example 1 contains propylene glycol and polyethylene glycol, which affect the viscosity of a liquid formulation. (Declaration, paragraph 5.) Viscosity impacts the spray plume geometry and droplet size of a nasal spray of the formulation, which, in turn, affects the T_{max} of midazolam when the formulation is administered intranasally. *Id.* However, the art cited in the Office action does not provide guidance on how polyethylene glycol will effect the T_{max} of a midazolam formulation. (Declaration, paragraph 6.) More particularly, the art cited in the Office action does not provide enough guidance to reasonably predict the T_{max} for Applicant's midazolam pharmaceutical composition as specified in claim 11. (Declaration, paragraph 6.)

In view of the foregoing, Applicant submits that the subject matter of amended claim 11, taken as a whole, would not have been obvious to the skilled artisan at the time the invention was made. Claim 11, as amended, requires propylene glycol, particular amounts of polyethylene glycol, and that the composition is formulated so that midazolam has "a time to maximum plasma concentration (T_{max}) within about 10 minutes after intranasal administration." The art cited in the Office action provides no guidance on how to select particular components or amounts of components in order to obtain a midazolam composition having "a time to maximum

plasma concentration (T_{max}) within about 10 minutes after intranasal administration." More particularly, as explained in the Declaration, the art cited in the Office action does not provide enough guidance to reasonably predict the T_{max} for Applicant's claimed midazolam pharmaceutical composition comprising from about 15 % to about 25 % by volume polyethylene glycol, and propylene glycol. For these reasons, Applicant respectfully requests that the rejection of claim 1 be reconsidered and withdrawn.

The comments above concerning claim 11 also apply to claim 12, which further specifies that the "polyethylene glycol comprises from about 15% to about 25% by volume and the propylene glycol constitutes from about 75% to about 85% by volume of the composition." In particular, the art cited in the Office action (i.e., Schweizer, Hjortkjaer, Haslwanter, Craig, Mukae, Fisgin, and Knoester) provides no guidance on whether compositions containing such high concentrations of propylene glycol and polyethylene glycol would be amenable to intranasal administration. Moreover, the art cited in the Office action provides no guidance as to what T_{max} one might get by intranasal administration of a composition containing such high concentrations of propylene glycol and polyethylene glycol.

Claims 13-15, 17, 18, 27, and 29 depend from and, therefore, incorporate all the limitations of claim 11. Claim 20 refers to the composition of claim 11, while claim 28 depends on claim 20. In view of the remarks relating to claim 11, Applicant respectfully requests that the rejection of claims 13-15, 17, 18, 20, and 27-29 also be reconsidered and withdrawn.

Double Patenting

According to pages 9-14 of the outstanding Office action, claims 11-18, 20, 27, and 28 presently stand rejected based on obviousness-type double patenting. In particular, claims 11-18, 20, 27, and 28 presently stand rejected for obviousness-type double patenting over certain claims of U.S. Patent No. 6,610,271. Claims 11-18, 20, 27, and 28 presently stand rejected for obviousness-type double patenting over certain claims of U.S. Patent Application Serial No. 11/376,979. Applicant respectfully requests that these rejections be held in abeyance until the instant claims are considered in condition for allowance but for these double patenting rejections.

At that time, Applicant plans to file terminal disclaimers, if the double patenting rejections are still considered to be appropriate.

Conclusion

Early favorable action is respectfully solicited. The Office is invited to contact the undersigned with any questions about this submission.

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Respectfully submitted,

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